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Objectives and Design of the Hemodialysis Fistula Maturation Study

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Abstract

Background—A large proportion of newly created arteriovenous fistulas cannot be used for dialysis because they fail to mature adequately to support the hemodialysis blood circuit. The Hemodialysis Fistula Maturation (HFM) Study was designed to elucidate clinical and biological factors associated with fistula maturation outcomes.

Study Design—Multicenter prospective cohort study.

Setting & Participants—Approximately 600 patients undergoing creation of a new hemodialysis fistula will be enrolled at 7 centers in the United States and followed up for as long as 4 years.

Predictors—Clinical, anatomical, biological, and process-of-care attributes identified pre-operatively, intra-operatively, or post-operatively.

Outcomes—The primary outcome is unassisted clinical maturation defined as successful use of the fistula for dialysis for four weeks without any maturation-enhancing procedures. Secondary outcomes include assisted clinical maturation, ultrasound-based anatomical maturation, fistula procedures, fistula abandonment, and central venous catheter use.

Measurements—Pre-operative ultrasound arterial and venous mapping, flow-mediated and nitroglycerin-mediated brachial artery dilation, arterial pulse wave velocity, and venous distensibility; intra-operative vein tissue collection for histopathological and molecular analyses; post-operative ultrasounds at 1 day, 2 weeks, 6 weeks, and prior to fistula intervention and initial cannulation.

Results—Assuming complete data, no covariate adjustment, and unassisted clinical maturation of 50%, there will be 80% power to detect ORs of 1.83 and 1.61 for dichotomous predictor variables with exposure prevalences of 20% and 50%, respectively.

Limitations—Exclusion of two-stage transposition fistulas limits generalizability. The requirement for study visits may result in a cohort that is healthier than the overall population of patients undergoing fistula creation.

Conclusions—The HFM Study will be of sufficient size and scope to 1) evaluate a broad range of mechanistic hypotheses, 2) identify clinical practices associated with maturation outcomes, 3) assess the predictive utility of early indicators of fistula outcome, and 4) establish targets for novel therapeutic interventions to improve fistula maturation.

Vascular access for maintenance hemodialysis is provided with an autogenous arteriovenous (AV) fistula, a synthetic AV graft, or a central venous catheter. The fistula is preferred because complication rates and health care expenditures are lower for patients with functioning fistulas than for those with synthetic grafts or central venous catheters[1]. Despite successful efforts to increase use of fistulas among patients undergoing maintenance hemodialysis, in the United States only approximately 60% of patients are dialyzed with a

fistula, and approximately 80% initiate maintenance dialysis treatment with a central venous catheter[2]. An important contributor to the low prevalence of fistulas is the failure of many newly created fistulas to mature adequately for use. Recent studies have documented maturation failure rates ranging from 20% to 60%[3–6].

Fistula maturation is a complex vascular remodeling process that requires vessel dilation, marked increases in blood flow rates in the feeding artery and draining vein, and structural changes in the vessel walls[7]. Our current understanding of these processes and the factors promoting and impeding successful maturation is limited. Major areas requiring research include identification of clinically useful pre-operative predictors of fistula outcome, elucidation of the pathophysiology of fistula maturation, identification of early post-operative indicators of fistula outcome, and development of interventions to facilitate maturation.

The Hemodialysis Fistula Maturation (HFM) Study is a multicenter prospective cohort study sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) designed to identify predictors of fistula maturation failure and elucidate underlying mechanisms. Study participants undergoing fistula creation surgery will be studied pre-operatively, intra-operatively, and post-operatively with collection of comprehensive clinical, anatomical, functional and pathological data using standardized procedures. This paper describes the objectives and design of the HFM Study, the mechanistic and translational investigations that will be conducted using HFM data and biosamples, and the potential applicability of the study findings to clinical practice and future clinical trials.

Study Rationale and Methods

Need for a Prospective Cohort Study

Development of interventions to improve fistula maturation outcomes has been hampered by a limited understanding of the underlying mechanisms. To date, only a small number of clinical trials of interventions to improve fistula maturation have been conducted. The Dialysis Access Consortium (DAC), also established by the NIDDK, performed a randomized placebo-controlled clinical trial which showed that clopidogrel prevented thrombosis of newly created fistulas but did not increase the proportion that could be used for dialysis[4]. Based in part on insights from this trial, the NIDDK recognized the need to learn more about processes of fistula maturation through a prospective, observational study. Although risk factors for fistula maturation failure have been identified through retrospective analyses of large databases and prospective cohort studies, these efforts have focused, in large part, on demographic and clinical factors that are not readily modifiable[6,8]. Given the complexity of the maturation process, elucidation of additional clinically useful and, especially, modifiable predictors of maturation failure requires a prospective study with 1) a sample size sufficiently large to allow statistical models that incorporate multiple risk factors and potential confounders, 2) data collection that is broad in scope, and 3) multiple outcome measures, including some that are closely linked to hypothesized biological processes and others chosen for their clinical relevance.

Objectives and Hypotheses of the HFM Study

The HFM Study is designed to identify predictors and underlying mechanisms of fistula maturation success and failure utilizing information from the following four domains:

1. Vascular anatomy before and after fistula creation.
2. Vascular biology characterized by functional, structural, and molecular assessments of vessels and systemic mediators before and shortly after fistula creation.
3. Clinical attributes of patients that might independently predict fistula outcomes, and potentially modify the associations of vascular anatomical and biological factors with fistula outcomes.
4. Processes of care that might independently predict fistula outcomes, and potentially modify the associations of vascular anatomical, biological, and clinical factors with fistula outcomes.

Each of these domains encompasses a set of hypothesized relationships between attributes and fistula outcomes that should be informative from a predictive and/or mechanistic standpoint (Table 1).

Composition of the Multidisciplinary HFM Study Group

The HFM protocol is being implemented by the HFM Study Group (see Acknowledgements), comprised of seven clinical centers; a Data Coordinating Center; core facilities for histopathology, ultrasound and vascular function testing; a study chair;, and NIDDK program scientists. The clinical centers are university-affiliated vascular access referral centers serving diverse patient populations in multiple U.S. geographic regions. Each clinical center has one or more surgical sites and ultrasound facilities, a vascular function testing facility, and multiple affiliated dialysis units. Clinical center principal investigators are nephrologists or vascular surgeons; co-investigators include nephrologists, vascular surgeons, transplant surgeons, cardiologists, pathologists, and radiologists. An independent External Expert Panel, appointed by the NIDDK, reviewed the protocol prior to implementation and monitors study progress.

Eligibility Criteria

The study is expected to enroll 600 participants undergoing creation of new fistulas. Participants are recruited from the nephrology and surgery practices of the participating centers utilizing center-specific strategies for identifying potential participants based upon local referral practices. Eligibility criteria are broad to maximize the generalizability of the findings (Box 1). To ensure ascertainment of clinical maturation, which requires fistula use, for individuals not yet receiving maintenance dialysis, eligibility for HFM requires 1) anticipated initiation of maintenance hemodialysis within 3 months after fistula creation and 2) age <80 years, to reduce the likelihood of death before dialysis initiation. Individuals for whom a two-stage fistula creation is planned, with distinct surgeries to create the AV anastomosis and to transpose the vein[9], are not eligible because of concern that differences in the maturation process and timing of cannulation would require separate, inadequately

powered analyses of fistulas created by one- and two-stage procedures. Thus, the findings of the study may not be generalizable to fistulas created via planned two-stage procedures.

Box 1

Eligibility Criteria

- Planned single-stage surgical creation of an autogenous upper-extremity fistula by a participating surgeon
- Current treatment with maintenance hemodialysis, or anticipated treatment with maintenance hemodialysis within 3 mo after planned fistula creation surgery
- Age < 80 y if not yet receiving treatment with maintenance hemodialysis; otherwise no upper age limit
- Life expectancy ≥ 9 mo
- Anticipated ability to comply with study procedures
- Ability to provide informed consent

Data Collection and Participant Follow-up

Collection of data and biosamples is summarized in Box 2. Prior to surgery all participants have ultrasound imaging of arteries and veins (vascular mapping) in the extremity to be used for fistula creation and non-invasive assessment of vascular function as described below. Information about surgical personnel, intra-operative and peri-operative medications, vessel and anastomosis sizes, procedure duration, anesthesia, and surgeon's assessment of fistula status prior to wound closure is obtained during surgery or immediately thereafter. Post-operative data include serial ultrasound measurements of fistula vessel diameter, depth, blood flow rate and other characteristics, and standardized information about fistula use, fistula procedures and complications related to either the study fistula or other vascular accesses. Blood samples are collected for DNA extraction, and for storage of serum and plasma, before and 2 weeks after fistula creation surgery. A unique feature of the study is the routine collection of a segment of the vein used for fistula creation immediately prior to creation of the AV anastomosis. Whenever feasible, a sample of fistula vein tissue is also collected during any surgical revisions.

Box 2

Data Collection and Study Procedures

Preoperative procedures

- Informed consent
- Eligibility screening
- Baseline clinical data collection
  - Demographics
  - Comorbidities
  - Medications
  - Dialysis history
  - Vascular access history

- Vascular-mapping ultrasound
- Vascular function studies
  - Brachial artery FMD/NMD
  - Arterial pulse wave velocity measurement
  - Venous occlusion plethysmography
- Blood collection for DNA, plasma and serum

Intraoperative procedures

- Surgical practices data collection
- Vein tissue collection
- End-of-surgery fistula status

Postoperative procedures

- Day-1 ultrasound
- 2-wk ultrasound and blood collection for plasma and serum
- 6-wk ultrasound
- [a] Precannulation ultrasound
- [b] Preprocedure ultrasound
- [c] 26-wk ultrasound
- Fistula cannulation data collection
- Clinical maturation assessment
- Vascular access complications and fistula procedures data collection
- Fistula use and abandonment data collection

Abbreviations: FMD, flow-mediated dilation; NMD, nitroglycerin-mediated dilation

[a] Pre-cannulation ultrasound is not performed if the first cannulation attempt occurs before 10 weeks.

[b] Pre-procedure ultrasound is performed only if the angioplasty or surgical procedure occurs before the pre-cannulation ultrasound.

[c] 26-week ultrasound is performed only if the pre-cannulation ultrasound has not yet been performed.

Post-operative study visits are required for scheduled ultrasounds and blood collection at defined time points. As with decisions related to fistula surgery, treating clinicians, rather than HFM Study personnel, make all decisions about fistula use and need for diagnostic and/or interventional procedures. Study personnel contact participants and their clinicians at least monthly to learn when initial fistula use is anticipated. Initial cannulation triggers more frequent monitoring to ascertain clinical maturation. After maturation is achieved, monthly contact is made to assess fistula durability and to continue to record fistula procedures and complications. Participants are followed up until the administrative end of the HFM Study. If a fistula is abandoned, the frequency of study contacts decreases to every six months.

Ultrasound studies—Pre-operative vascular mapping and post-operative fistula ultrasounds are performed by personnel trained by the HFM Ultrasound Core using standardized protocols, and all images are read centrally by core radiologists[10]. Pre-operative vascular mapping results are also read locally for clinical use; however, consistent with standard care at participating sites, the post-operative study ultrasounds are not made

available to local clinicians or study investigators unless there is a finding that threatens the participant's health (e.g., impending rupture of pseudoaneurysm). If standard care at a clinical center includes an ultrasound 6 weeks after surgery, the HFM 6-week ultrasound is made available for local reading and interpretation. The serial post-operative ultrasounds will serve multiple functions including characterizing the natural history of fistula maturation and delineating temporal changes that reflect physiological responses to fistula creation (Table 2). One HFM Study objective is to determine the utility of fistula blood flow rate and luminal diameter measurements as surrogates, or components of composite surrogate outcomes, for fistula usability (Table 1)[11].

Vascular function studies—Vascular function studies using the arm in which the fistula will be created are performed before fistula creation by study personnel trained by the Vascular Function Core using standardized procedures and equipment. These measurements include 1) flow-mediated and nitroglycerin-mediated brachial artery dilation to assess endothelium-dependent and endothelium-independent functions, respectively, 2) carotid-femoral and carotid-radial pulse wave velocity to assess stiffness of the aorta and conduit arteries of upper extremity, respectively, and 3) venous distensibility assessed with venous occlusion plethysmography[12–14]. If completion of at least two of the three types of vascular function studies is not possible, the participant is not followed up further and is replaced to achieve the target sample size. Flow-mediated dilation and nitroglycerin-mediated dilation ultrasound images are analyzed centrally by the Vascular Function Core.

Vein tissue processing and storage—An intact 5- to 10-mm long segment of the vein used for the fistula anastomosis is excised during surgery, immediately divided into 4 pieces and placed into 1) formalin, 2) ribonuclease inhibitors, 3) liquid nitrogen, and 4) proteomic buffer. The tissue is used to identify structural, cellular, and local molecular markers associated with fistula outcomes. The extent of pre-existing intimal hyperplasia will be evaluated using histology and morphometry. Immunohistochemistry will be used for cellular phenotyping and to identify markers of molecular pathways including those associated with cell proliferation, apoptosis, inflammation, matrix deposition and calcification. Samples are stored at the NIDDK Biospecimen Repository (www.niddkrepository.org) for gene expression studies, laser capture micro-dissection of specific cell types or extracellular material, and proteomic analyses.

Study Outcomes

The primary study outcome is unassisted clinical maturation, defined as fistula use with two needles for ≥75% of dialysis sessions over a continuous 4-week period and either:

1. Four consecutive sessions during the 4-week period in which two needles are used and the mean dialysis machine blood pump speed is ≥300 ml/min, or
2. A measured single-pool Kt/V ≥1.4 or urea reduction ratio >70% during any session in which two needles are used within the 4-week period. Single-pool Kt/V is calculated from pre- and post-treatment serum urea nitrogen concentrations, body weight, and dialysis session duration.

The clinical maturation criteria can be satisfied at any time within 9 months of fistula creation surgery or within 8 weeks of dialysis initiation, whichever comes later. The 8-week period after dialysis initiation accommodates initial fistula use with small gauge needles and low machine pump speeds, as practiced at many facilities. For “unassisted” maturation, the criteria must be met before any endovascular or surgical procedure on the fistula.

As detailed in Box 3, other outcomes include:

1. Additional fistula use outcomes: assisted clinical maturation (satisfaction of the aforementioned criteria after a procedure to facilitate maturation), post-surgical time to successful cannulation, clinical usability, and fistula abandonment.
2. Anatomical characteristics: fistula blood flow and vessel diameter as assessed by ultrasound.
3. Fistula complications: stenosis, thrombosis, hand ischemia, aneurysm or pseudoaneurysm, infiltration, and central venous catheter use.
4. Fistula procedures and procedures on other vascular accesses: angioplasty, surgical revision, stent placement, and ligation of accessory veins.
5. Clinical events: bloodstream infections, vascular access-related hospitalizations, and death.

Box 3

Outcomes

Primary outcome
Unassisted clinical maturation defined as:

- Use of fistula with 2 needles for 75% of dialysis sessions during a 4-wk period with either:
  1. 4 consecutive dialysis sessions with mean blood pump speed ≥ 300 ml/min, or
  2. Single-pool Kt/V ≥1.4 or urea reduction ratio >70%
- Criteria must be met without any fistula intervention procedures and by the later of 9 mo after surgery or 8 wk after dialysis initiation

Additional fistula use outcomes

- Assisted clinical maturation defined as clinical maturation following a maturation-facilitating procedure
- First cannulation attempt
- First successful cannulation defined as the use of the fistula with 2 needles and for the entire dialysis session
- Fistula durability defined as the number of months of use of the fistula for dialysis
- Fistula abandonment defined as the date at which the treating nephrologist or surgeon determines that the fistula will not be used in the future.

Anatomical (sonographic) outcomes

- Fistula blood flow rate
- Fistula artery diameter
- Fistula vein diameter
- Vein depth from skin surface

- Stenosis

Fistula events

- Thrombosis
- Hand ischemia infiltration
- Fistula bleeding
- Pseudoaneurysm or aneurysm requiring a procedure
- Infection

Fistula or other access procedures

- Angioplasty
- Surgical revision
- Stent placement
- Thrombolysis or thrombectomy
- Ligation of accessory veins
- Superficialization of vein
- Transposition of vein
- Central venous catheter placement
- Placement of new arteriovenous access

Clinical events

- Bloodstream infection
- Vascular access–related hospitalization
- Death

Data Analysis and Statistical Power

The general analytical approach will be to evaluate associations between predictor variables and outcomes using multiple linear and logistic mixed-effects regression models. To account for the clustered structure of the data, these models will include fixed or random hospital effects and random surgeon effects. Analyses of serial ultrasound trajectories will also include either random patient effects or a time series covariance structure. Several combinations of optimization criteria and fitting algorithms will be used for logistic mixed models depending on analytic objectives, dataset structure, sample size, and model complexity. Full likelihoods will be optimized when feasible, using marginal approaches (which approximate averaging over random effects) where needed. Associations of fistula outcomes with predictors will be treated as uniform across all fistula anatomical configurations unless there is strong statistical or biological evidence to suggest otherwise. Splines will be introduced into models to assess for nonlinearity, and cross product terms for effect modification. Receiver operating characteristic curves and measures of classification accuracy will be used to compare alternative prediction models for dichotomous outcomes, including evaluation of postoperative ultrasound parameters as predictors and potential surrogates for clinical maturation.

Formal analysis planning will be used to limit false positive findings from analyses of multiple candidate predictors and outcomes, although the requirement for planning will be less stringent than is usual for pivotal clinical trials. For example, when the scientific context allows choices among candidate predictors or potential confounders in a given domain (e.g., vascular function), “first priority” variables or variable subsets for inclusion will be pre-specified without reference to the outcome data. These choices will be based on clinical and biological considerations, frequency of use in other published studies, information about measurement reliability and validity, and emerging variability and correlations among each domain’s candidate predictors in HFM Study data.

The adequacy of the sample size was assessed by estimating minimum detectable odds ratios (ORs) for primary mixed logistic regression analyses of unassisted clinical maturation incorporating assumptions that 40% of participants will enroll before dialysis initiation, that outcome ascertainment will not be possible for 15% of participants who enroll prior to initiation of dialysis and for 4% of participants receiving dialysis treatment at enrollment, and under varying other assumptions. For example, for a dichotomous predictor uncorrelated with other covariates including surgeon effects, and with 50% prevalence in study participants, ORs of 1.75 and 1.61 are detectable with 90% and 80% power, respectively. In the simple case of no covariates, these ORs correspond to risk ratios of 1.27 and 1.32. The respective ORs increase to approximately 2.01 and 1.83 for a less prevalent exposure present in 20% of participants, or an exposure more highly correlated (R = 0.6) with covariates.

Discussion

To our knowledge, the HFM Study is the first multi-center prospective epidemiological study of fistula maturation conducted in the U.S. Because the study is observational, it allows examination of multiple factors thought to affect fistula maturation within the setting of usual care. The study brings together clinical and translational investigators in nephrology, surgery, vascular medicine, radiology, pathology, epidemiology and biostatistics to collect prospectively detailed clinical data, imaging data, functional assessments, and biospecimens to identify predictors and underlying mechanisms of hemodialysis fistula maturation. The HFM Study was designed to be of sufficient size and scope to evaluate a broad group of inter-related hypotheses. By identifying targets for novel interventions and by evaluating the adequacy of alternative outcome measures, the study should facilitate the design and conduct of future clinical trials.

Much of the previous fistula maturation research has focused on clinical and demographic predictors which are largely non-modifiable and have not adequately explained fistula outcomes[6,8]. The HFM Study incorporates anatomical and functional characteristics of the vessels, surgical approaches and intra-operative events, and pre-operative and post-operative processes of care. Unlike prior studies relating vessel anatomy to maturation outcomes, the HFM Study distinguishes lumen (inner) diameter from vessel (outer) diameter and evaluates arterial blood flow rate[15–17].

Endothelial dysfunction and vascular stiffness are often present in patients with end-stage renal disease[18–20,21,22]. We hypothesize that pre-existing abnormalities in endothelial

function, vascular smooth muscle cell function, arterial compliance, and venous distension interfere with the immediate arterial and venous dilation and the more protracted vessel remodeling necessary for successful fistula maturation[7]. The comprehensive assessment of vascular function using *in vivo* measurements prior to fistula creation is unique to the HFM Study. One previous study assessed the relationship between venous capacitance and fistula maturation, and another evaluated the association between arterial elasticity and fistula outcome; however these studies, each of which included approximately 30 patients, were too small to adequately address inherent variability of the vascular function assessments and adjust for confounding by clinical factors[23,24]. Unlike prior studies, the HFM Study will utilize a broad array of measurements that provide information about arteries and veins, vessels of varying sizes, and both endothelium-dependent (flow-mediated dilation) and endothelium-independent (nitroglycerin-mediated dilation) processes.

Histology, morphometry, immunostaining, and gene expression analyses of vein tissue obtained during fistula creation will provide information that complements and adds granularity to the findings from the *in vivo* evaluations of vascular function. There is a strong theoretical basis and suggestive evidence from animal models for hypothesizing that processes such as oxidative stress, inflammation, intimal hyperplasia, extracellular matrix alterations, calcification, and matrix metalloproteinase activity contribute to fistula maturation failure[25–33]; HFM samples provide a resource for relevant data from humans, which are currently limited to a few small studies[34–39].

Surgical training and techniques, and post-operative management of fistulas, are widely viewed to be important determinants of fistula outcomes. The HFM Study will provide the multi-center, patient-level detail that is necessary, but lacking in previous studies, to adequately address specific hypotheses and guide recommendations for clinical practice[40–43].

The clinical maturation criteria were developed with the goal of creating an outcome that is 1) highly clinically relevant, 2) uniformly ascertainable, and 3) relatively unaffected by variation in dialysis facility or clinician practices such as timing of initial use of a fistula. The requirement that the fistula support a minimum dialysis machine pump speed of 300 ml/min was incorporated because most patients need this pump speed to achieve sufficient small-solute clearance during the 3- to 4.5-hour dialysis sessions typically used for maintenance hemodialysis in the U.S. A single-pool Kt/V threshold of 1.4 was provided as an alternative criterion because lower blood pump speeds can provide adequate urea clearance for individuals with a low urea volume of distribution or for those prescribed prolonged dialysis treatment times. The requirement for only 4 weeks of use was based on the intent to capture fistula maturation rather than fistula durability. Because fistula use is dependent not only on adequate maturation but also on the technical skills of the individuals performing cannulation, the clinical maturation criteria allow for occasional inability to use the fistula. A liberal time frame was selected for clinical maturation attainment in recognition of the broad range of clinical practices for initiating fistula use.

Importantly, although the HFM Study has a pre-specified definition of clinical maturation, the data collection scheme will allow evaluation of alternative maturation criteria. For

example, four weeks of fistula use without a dialysis machine pump speed or solute clearance threshold, or fistula use within 3 months rather than 9 months after fistula creation, might be highly correlated with the more complex primary outcome of the HFM Study. One of the study objectives is to determine whether criteria that require less intensive data collection or shorter follow-up can accurately classify outcomes based on more complete follow-up.

The HFM Study provides an infrastructure and dataset that can be utilized for ancillary investigations to expand the scientific scope of the study. Several externally funded ancillary studies have been initiated including (1) examination of fistula mechanical shear stress using magnetic resonance imaging coupled with computational flow dynamics, (2) functional characterization of vascular smooth muscle cells, (3) real-time measurement of circulating nitric oxide, (4) measurement of markers of mineral metabolism, and (5) genomic analyses. After the HFM Study is completed, the dataset, biosamples, ultrasound images, and vascular function measurements will be maintained in the NIDDK Data and Biosample Repositories and will be accessible to the broad community of investigators.

The HFM Study has multiple objectives, each relevant to patient care. Identifying clinically available pre-operative predictors of fistula maturation outcomes will inform patient-level decisions about the type of vascular access to create. Characterizing relationships between clinical practices and fistula outcomes should generate testable hypotheses that can be evaluated with quality improvement programs or controlled clinical trials. Early ultrasound indicators of maturation failure might guide use of maturation-enhancing interventions or trigger earlier revision or replacement of failing fistulas, thereby decreasing the duration and associated morbidity of central venous catheter use.[44]. Additionally, if they have sufficient predictive utility, ultrasound surrogates for clinical maturation or simplification of clinical maturation outcome measures should facilitate the development and evaluation of new interventions by decreasing the required duration, sample size, and/or costs of future clinical trials. Finally, functional, structural and molecular characterization of the vasculature linked to subsequent anatomical and usability outcomes will allow evaluation of a broad range of mechanistic hypotheses that could identify targets for therapeutic interventions. Thus, we anticipate that the HFM Study will make important contributions to both the understanding of the pathophysiology of fistula maturation and the clinical care of patients treated with maintenance hemodialysis.

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Table 1

Major Hypotheses of the HFM Study by Domain

Hypotheses	Anticipated Utility
Vascular Anatomy	
Anatomical characteristics of vessels such as diameter prior to fistula creation are determinants of fistula maturation	Clinical[1], Mechanistic[2]
Early post-operative changes in fistula blood flow rate and vessel diameter predict fistula maturation outcomes	Clinical, Mechanistic
Serial post-operative ultrasounds can identify anatomical lesions associated with fistula maturation failure	Clinical, Mechanistic, Therapeutic targets[3]
Blood flow rate and luminal diameter determined by ultrasound can serve as surrogates for fistula usability	Research tool[4]
Vascular Biology	
Functional, structural and molecular characteristics of vessels prior to fistula creation are determinants of fistula maturation	Mechanistic, Therapeutic targets
Vascular function and tissue characteristics prior to fistula creation are associated with early post-operative changes in blood flow rate and vessel diameter	Mechanistic, Therapeutic targets
Circulating blood factors reflecting inflammation and oxidative stress are associated with fistula maturation outcomes	Mechanistic, Therapeutic targets
Post-operative changes in circulating biomarkers correlate with early post-operative changes in blood flow rate, vessel diameter and fistula usability	Mechanistic, Therapeutic targets
Clinical Attributes	
Patient demographics, comorbidities, and medications are associated with fistula maturation but have limited predictive utility without additional measures that reflect vascular physiology and biology	Clinical
Patient demographics, comorbidities, and medications are associated with pre-operative vascular anatomy and biology	Mechanistic, Therapeutic targets
Patient demographics, comorbidities, and medications are associated with post-operative changes in blood flow rate and vessel diameter	Mechanistic
Processes of Care	
Surgical practices such as size of anastomosis are associated with fistula maturation outcomes	Clinical
Dialysis practices such as timing of cannulation are associated with fistula outcomes	Clinical

HFM, Hemodialysis Fistula Maturation.

[1]Clinical: might have implications for decisions about attempting fistula creation or about management of fistulas

[2]Mechanistic: might provide information relevant to specific hypothesized mechanisms of maturation failure

[3]Therapeutic targets: might identify therapeutic targets for development or testing

[4]Research tool: might identify an endpoint for research studies

Table 2

Purpose of Post-Operative Ultrasound Measurements

Time from Fistula Creation	Purpose
Day 1	Characterize vascular response immediately after fistula creation; predict anatomical or clinical maturation
2 wk	Characterize vascular response early after fistula creation; predict anatomical or clinical maturation
6 wk	Predict clinical maturation; potential surrogate for clinical maturation
Prior to first cannulation of fistula; prior to first intervention if fistula not previously cannulated; prior to 26 wk if fistula not previously cannulated	Correlate anatomical features with clinical maturation; explain potential discrepancies between 6-wk (and 26-wk) ultrasound findings and clinical maturation